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Cancer Research

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Michael Platten, Wolfgang Wick, and Benoit J. Van den Eynde
- 5441 | **Purines, Purinergic Receptors, and Cancer**
Francesco Di Virgilio

PRIORITY REPORT

- 5448 | **CDK1 Regulates Mediator of DNA Damage Checkpoint 1 during Mitotic DNA Damage**
Bing Yu, W. Brian Dalton, and Vincent W. Yang
- Précis:* This study defines a fundamental step in the response to DNA damage and its repair in mitosis, which appears to function aberrantly in cancer cells, perhaps universally.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 5454 | **Ploidy and Large-Scale Genomic Instability Consistently Identify Basal-like Breast Carcinomas with *BRCA1/2* Inactivation**
Tatiana Popova, Elodie Manié, Guillaume Rieunier, Virginie Caux-Moncoutier, Carole Tirapo, Thierry Dubois, Olivier Delattre, Brigitte Sigal-Zafrani, Marc Bollet, Michel Longy, Claude Houdayer, Xavier Sastre-Garau, Anne Vincent-Salomon, Dominique Stoppa-Lyonnet, and Marc-Henri Stern
- Précis:* The SNP-array-based genomic signature of *BRCA1/2* inactivation in basal-like breast carcinoma described in this study may greatly ease the practical challenges of selecting patients for genetic testing or for recruitment to clinical trials of emerging therapies that target DNA repair deficiencies in cancer.

MICROENVIRONMENT AND IMMUNOLOGY

- 5463 | **MiR-10b Downregulates the Stress-Induced Cell Surface Molecule MICB, a Critical Ligand for Cancer Cell Recognition by Natural Killer Cells**
Pinchas Tsukerman, Noam Stern-Ginossar, Chamutal Gur, Ariella Glasner, Daphna Nachmani, Yoav Bauman, Rachel Yamin, Alon Vitenshtein, Noah Stanietsky, Tomer Bar-Mag, Dikla Lankry, and Ofer Mandelboim
- Précis:* These findings show how upregulation of an important metastasis-promoting microRNA in cancer cells also permits them to evade natural killer cells, thereby linking metastatic capability and immune escape.
- 5473 | **T-Cell Trafficking Facilitated by High Endothelial Venules Is Required for Tumor Control after Regulatory T-Cell Depletion**
James P. Hindley, Emma Jones, Kathryn Smart, Hayley Bridgeman, Sarah N. Lauder, Beatrice Ondondo, Scott Cutting, Kristin Ladell, Katherine K. Wynn, David Withers, David A. Price, Ann Ager, Andrew J. Godkin, and Awen M. Gallimore
- Précis:* This seminal study defines a new function for tumor-supportive regulatory T cells, known informally as Tregs, in inhibiting the development in tumors of a specialized form of blood vessel that facilitates immune cell recruitment but is normally confined to lymph nodes.
- 5483 | **Autophagy Induced by Conventional Chemotherapy Mediates Tumor Cell Sensitivity to Immunotherapy**
Rupal Ramakrishnan, Chun Huang, Hyun-II Cho, Mark Lloyd, Joseph Johnson, Xiubao Ren, Soner Altioek, Daniel Sullivan, Jeffrey Weber, Esteban Celis, and Dmitry I. Gabrilovich
- Précis:* Chemotherapy harms the innate immune system but actually appears to stimulate the adaptive immune system at some level, including by activating autophagy, helping explain why chemotherapy may be efficacious and why it should cooperate with immunotherapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 5494 **IKK-ε Coordinates Invasion and Metastasis of Ovarian Cancer**
Sarah Hsu, Marianne Kim, Lidia Hernandez, Valentina Grajales, Anne Noonan, Miriam Anver, Ben Davidson, and Christina M. Annunziata

Précis: This study suggests that a less studied isoform of the NF-κB regulatory subunit family is a rational target for therapeutic attack in ovarian cancers, where it appears to be aberrantly activated.

- 5505 **Iodide Transporter NIS Regulates Cancer Cell Motility and Invasiveness by Interacting with the Rho Guanine Nucleotide Exchange Factor LARG**

Claire Lacoste, Julie Hervé, Myriam Bou Nader, Alexandre Dos Santos, Nicolas Moniaux, Yannick Valogne, Rodrick Montjean, Olivier Dorseuil, Didier Samuel, Doris Cassio, Carla Portulano, Nancy Carrasco, Christian Bréchet, and Jamila Faivre

Précis: This study takes an important step toward elucidating the link between the iodide transporter and nonthyroid carcinogenesis, casting a new light on how solute-linked carrier proteins contribute to cancer biology.

- 5516 **RhoJ Regulates Melanoma Chemoresistance by Suppressing Pathways That Sense DNA Damage**

Hsiang Ho, Jayavani Aruri, Rubina Kapadia, Hootan Mehr, Michael A. White, and Anand K. Ganesan

Précis: The basis for enhanced chemoresistance of melanoma cells is traced to a Rho signaling pathway that may offer a rational strategy for improving the efficacy of chemotherapy regimens in treating advanced melanoma, which remains clinically problematic.

- 5529 **Microdistribution and Long-term Retention of ²³⁹Pu (NO₃)₄ in the Respiratory Tracts of an Acutely Exposed Plutonium Worker and Experimental Beagle Dogs**

Christopher E. Nielsen, Dulaney A. Wilson, Antone L. Brooks, Stacey L. McCord, Gerald E. Dagle, Anthony C. James, Sergei Y. Tolmachev, Brian D. Thrall, and William F. Morgan

Précis: The retention of soluble plutonium within connective scar tissue in human lungs and in the lungs of experimental beagle dogs minimizes cancer risk by preventing the irradiation of sensitive epithelial cells.

PREVENTION AND EPIDEMIOLOGY

- 5537 **Genetic Polymorphisms and Protein Expression of NRF2 and Sulfiredoxin Predict Survival Outcomes in Breast Cancer**

Jaana M. Hartikainen, Maria Tengström, Veli-Matti Kosma, Vuokko L. Kinnula, Arto Mannermaa, and Ylermi Soini

Précis: Potentially seminal findings identify biomarkers in a core ROS stress pathway that may be generally impactful in determining the survival outcomes of patients with breast cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 5547 **Targeting BRCA1 Localization to Augment Breast Tumor Sensitivity to Poly(ADP-Ribose) Polymerase Inhibition**

Eddy S. Yang, Somaira Newsheen, Mohammad A. Rahman, Rebecca S. Cook, and Fen Xia

Précis: Breast cancer sensitivity to PARP inhibitors can be conferred by therapeutic tactics that can mislocalize BRCA1 to the cancer cell cytosol.

- 5556 **CD22 Antigen Is Broadly Expressed on Lung Cancer Cells and Is a Target for Antibody-Based Therapy**

Joseph M. Tuscano, Jason Kato, David Pearson, Chengyi Xiong, Laura Newell, Yungpeng Ma, David R. Gandara, and Robert T. O'Donnell

Précis: A cell adhesion molecule that had been thought to be confined in expression to B cells is also expressed in many lung cancer cells, where existing antibodies to the molecule can exert potent antitumor and antimetastatic properties, calling for prompt evaluation in clinical trials.

- 5566 **Overcoming Limitations in Nanoparticle Drug Delivery: Triggered, Intravascular Release to Improve Drug Penetration into Tumors**

Ashley A. Manzoor, Lars H. Lindner, Chelsea D. Landon, Ji-Young Park, Andrew J. Simnick, Matthew R. Dreher, Shiva Das, Gabi Hanna, Won Park, Ashutosh Chilkoti, Gerben A. Koning, Timo L.M. ten Hagen, David Needham, and Mark W. Dewhirst

Précis: This article suggests a straightforward and widely applicable solution to one of the core problems in nanoparticle-based therapeutic approaches, which is the pharmacologic problem of how to specifically and efficiently deliver cargo to tumor cells.

5576 | **miRNA-34 Prevents Cancer Initiation and Progression in a Therapeutically Resistant K-ras and p53-Induced Mouse Model of Lung Adenocarcinoma**

Andrea L. Kasinski and Frank J. Slack

Précis: This preclinical study demonstrates the efficacy of using a single microRNA to impair lung tumorigenesis in an aggressive autochthonous mouse model of non-small cell lung cancer.

5588 | **Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors**

Junko Murai, Shar-yin N. Huang, Benu Brata Das, Amelie Renaud, Yiping Zhang, James H. Doroshow, Jiuping Ji, Shunichi Takeda, and Yves Pommier

Précis: These findings indicate that PARP inhibitors in clinical trials not only block catalytic function but also trap PARP enzymes on DNA, illuminating the mechanistic basis for their cytotoxic activity in cancer cells.

5613 | **Control of Breast Cancer Growth and Initiation by the Stem Cell-Associated Transcription Factor TCF3**

Michal Slyper, Amit Shahar, Anat Bar-Ziv, Roy Z. Granit, Tamar Hamburger, Bella Maly, Tamar Peretz, and Ittai Ben-Porath

Précis: These findings establish an important role in aggressive breast cancer for a central regulator of normal stem cell function.

5625 | **Cross-talk between HER2 and MED1 Regulates Tamoxifen Resistance of Human Breast Cancer Cells**

Jiajun Cui, Katherine Germer, Tianying Wu, Jiang Wang, Jia Luo, Shao-chun Wang, Qianben Wang, and Xiaoting Zhang

Précis: This important study defines an estrogen receptor (ER) coactivator that plays a central role in mediating tamoxifen resistance in human breast cancer, addressing a widespread issue arising in the management of ER-positive breast cancer patients.

TUMOR AND STEM CELL BIOLOGY

5600 | **CD24 Is an Effector of HIF-1-Driven Primary Tumor Growth and Metastasis**

Shibu Thomas, Michael A. Harding, Steven C. Smith, Jonathan B. Overvest, Matthew D. Nitz, Henry F. Frierson, Scott A. Tomlins, Glen Kristiansen, and Dan Theodorescu

Précis: This important study connects the function of 2 molecules of seminal importance in cancer biology and strengthens the rationale to target the stem cell-associated surface molecule CD24 for cancer therapy.

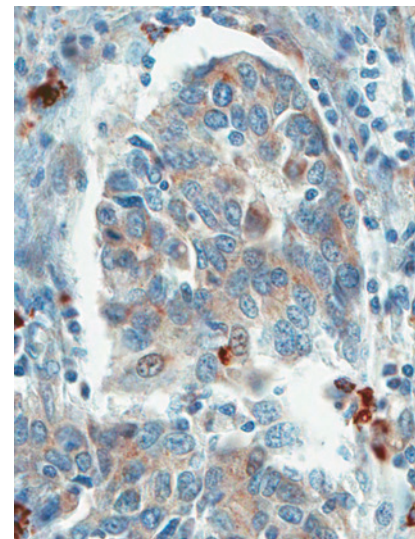
5635 | **Multiple Roles of p53-Related Pathways in Somatic Cell Reprogramming and Stem Cell Differentiation**

Lan Yi, Chiwei Lu, Wenwei Hu, Yvonne Sun, and Arnold J. Levine

Précis: These findings deepen insights into the potent effects of p53 on stem cell prowess, which may yet prove to be of great importance in understanding not only the roots of cancer but also how to eradicate it.

ABOUT THE COVER

The GPI-linked cell surface glycoprotein, CD24, has been shown to be a biomarker of and contributor to carcinogenesis and metastasis in several tumor types. The transcription factor, HIF-1 α , plays a key role in physiologic and neoplastic hypoxia, regulating expression of several oncogenic transcriptional targets. Herein, Thomas and colleagues provide a mechanistic link between these two key proteins in cancer biology by showing that HIF-1 α directly regulates CD24 at its promoter and that the prometastatic activity of HIF-1 α in experimental metastasis models of bladder and prostate cancer depends on CD24 expression. Immunohistochemical studies using human bladder cancer tissues (pictured on cover) found that expression of HIF-1 α and CD24 was correlated, whereas simultaneous low expression of these biomarkers was associated with the best overall patient survival, supporting the clinical relevance of this pathway. For details, see article by Thomas and colleagues on page 5600.



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